

## Daily 500 mg Valacyclovir Is Effective for Prevention of Varicella Zoster Virus Reactivation in Patients with Multiple Myeloma Treated with Bortezomib

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**Abstract.** *Background:* In patients with multiple myeloma (MM), bortezomib is associated with a significant risk of Varicella zoster virus (VZV) reactivation. There are some reports that acyclovir reduces the risk of VZV reactivation. We assessed whether VZV reactivation could be reduced by using prophylactic valacyclovir at a dose of 500 mg daily. *Patients and Methods:* We retrospectively evaluated 32 patients with MM who received bortezomib and valacyclovir prophylaxis at the Kanazawa Medical University Hospital. Patients received valacyclovir prophylaxis orally at a dose of 500 mg daily, without cessation during bortezomib treatment. *Results:* The median age was 69 years (range=45-90 years). Fifteen patients were male and seventeen were female. The median bortezomib dose was 37.0 mg/m<sup>2</sup> (range=5.2-167.6 mg/m<sup>2</sup>). All patients also received corticosteroids. The median duration of valacyclovir prophylaxis was 301 days (range=24-1206 days) and the median valacyclovir dose was 150.5 g (range=12-603 g). VZV reactivation developed in only one patient during valacyclovir prophylaxis. VZV reactivation did not develop in three patients who had a past history of VZV reactivation without valacyclovir prophylaxis. Adverse events over grade 3 associated with valacyclovir were not observed. *Conclusion:* Valacyclovir at a dose of 500 mg daily appears to be effective at preventing VZV reactivation and was well-tolerated by patients with MM who received bortezomib.

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*Key Words:* Multiple myeloma, bortezomib, varicella zoster virus, valacyclovir, acyclovir.

Multiple myeloma (MM) is a hematological malignancy characterized by monoclonal proliferation of plasma cells and the presence of monoclonal immunoglobulin in the serum and urine. Its common clinical features are anemia, renal dysfunction, osteolysis and hypercalcemia (1-3). In the past decade, there have been major advances as a result of new anti-myeloma agents (2, 3). A proteasome inhibitor, bortezomib, is one of these new agents (4, 5) and has been successfully used for the treatment of MM (2, 3, 6-10). On the other hand, the use of bortezomib is associated with some adverse events. Varicella zoster virus (VZV) reactivation (herpes zoster) is one adverse event of bortezomib therapy (11). In the Assessment of Proteasome Inhibitor for Extending Remission (APEX) trial, bortezomib was associated with a significant higher incidence of VZV reactivation when compared with dexamethasone treatment (13% vs. 5%,  $p=0.0002$ ) in patients with relapsed MM (12). In the Velcade as Initial Standard Therapy in Multiple Myeloma: Assessment with Melphalan and Prednisone (VISTA) trial, the incidence was more frequent in the bortezomib-melphalan-prednisolone therapy group than in the melphalan-prednisolone therapy group (13% vs. 4%) for initial treatment for MM (8). On the other hand, there are some reports that acyclovir reduces the risk of VZV reactivation (8, 13-17). National Comprehensive Cancer Network (NCCN) guidelines for prevention and treatment of cancer-related infections recommend prophylaxis for VZV reactivation in patients treated with bortezomib (18). To determine whether VZV reactivation could be reduced by using prophylactic valacyclovir at a dose of 500 mg daily, we retrospectively evaluated data from 32 patients with MM who received bortezomib and valacyclovir prophylaxis at our institute.

### Patients and Methods

*Patients.* We retrospectively analyzed the medical records of 32 patients with MM who received bortezomib and valacyclovir prophylaxis at the Kanazawa Medical University Hospital between

Table I. Characteristics of patients (n=32).

Characteristic	Value
Age, years	
Median	69
Range	45-90
Gender	
Male	15
Female	17
Type of M-protein	
IgG	18
IgA	5
IgD	2
Bence-Jones	7
International Staging System	
1	8
2	8
3	16
ECOG performance status	
1	4
2	16
3	12
Time to bortezomib therapy from diagnosis (months)	
Median	4.5
Range	1-180
Number of prior therapies	
0	1
1	17
2	11
4	2
5	1

ECOG, Eastern Cooperative Oncology Group.

January 2007 and April 2012. The diagnosis of MM was confirmed using the International Myeloma Working Group criteria (1). The clinical stage was determined by the International Staging System (19).

**Bortezomib treatment.** Patients received 1.0-1.3 mg/m<sup>2</sup> bortezomib as an intravenous bolus with corticosteroids. Some patients received this in combination with other anti-myeloma agents. Bortezomib was continued until achieving a complete response, disease progression, the development of severe adverse events, or undergoing hematopoietic stem cell collection by high-dose cyclophosphamide.

**Valacyclovir prophylaxis for VZV reactivation.** Patients received valacyclovir prophylaxis orally at a dose of 500 mg daily without cessation during bortezomib treatment. Adverse events were graded using the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 3.0 (20).

## Results

**Patients' characteristics.** Table I shows the characteristics of the 32 patients. The median time from diagnosis to starting bortezomib therapy was 4.5 months (range=1-180 months). All patients except one had received prior therapy for MM. The median number of prior therapies was 1 (range=0-5;

Table II. Patients distribution according to bortezomib-containing regimen (n=32).

Regimens	No. of patients
BD	24
VMP	1
BD + VMP	3
BD + iPAD	1
BD + VCD	2
iPAD + VCD	1

BD, Bortezomib plus dexamethasone; VMP, bortezomib plus melphalan plus prednisolone; iPAD, bortezomib plus doxorubicin plus intermediate-dose dexamethasone; VCD, bortezomib plus cyclophosphamide plus dexamethasone.

radiotherapy was counted as one regimen). Thirty patients had received corticosteroids; eleven had received corticosteroids-alone. Eighteen had received melphalan-containing therapy. Four had received thalidomide or lenalidomide. Three had undergone radiotherapy.

**Bortezomib treatment.** Table II shows the number of patients who received bortezomib-containing regimens. Bortezomib plus dexamethasone (BD) therapy included twice-weekly BD therapy (on days 1, 4, 8 and 11 in a 3-week cycle), once-weekly BD therapy (on days 1, 8, 15 and 22 in a 5-week cycle) and maintenance (once- to twice-monthly administration). The median bortezomib dose was 37.0 mg/m<sup>2</sup> (range=5.2-167.6 mg/m<sup>2</sup>).

**Valacyclovir prophylaxis for VZV reactivation.** Twenty-eight patients received valacyclovir prophylaxis since the first administration of bortezomib, one patient since the third course of BD therapy and three patients since re-administration of bortezomib after relapse of their MM. Three out of four patients who had not received valacyclovir prophylaxis since the first administration of bortezomib had a past history of VZV reactivation without valacyclovir prophylaxis. In two patients with renal dysfunction, the doses of valacyclovir were reduced to 250 mg daily. The median duration of valacyclovir prophylaxis was 301 days (range=24-1206 days) and the median valacyclovir dose was 150.5 g (range=12-603 g). VZV reactivation (grade 2 herpes zoster) developed in only one female patient during valacyclovir prophylaxis. Herpes zoster was localized on the skin of her left leg and was cured without post-herpetic neuralgia by a therapeutic dosage of valacyclovir. She was then able to receive bortezomib-containing chemotherapy again. In another patient, VZV reactivation was developed 100 days after the cessation of bortezomib treatment and valacyclovir prophylaxis. VZV reactivation did not develop in three patients who had a past history of VZV reactivation without valacyclovir prophylaxis. Adverse events over grade 3 associated with valacyclovir were not observed.

## Discussion

Our study demonstrated that daily 500 mg valacyclovir is effective at preventing VZV reactivation and is well-tolerated in patients with MM who received bortezomib. Daily 500 mg valacyclovir prophylaxis is also effective for patients who have had heavy prior therapies and for patients with poor PS.

In the APEX trial, bortezomib therapy was associated with a significant higher incidence of VZV reactivation when compared with dexamethasone treatment (13% *vs.* 5%,  $p=0.0002$ ) in patients with relapsed MM. The median time to the onset of herpes zoster was shorter with bortezomib than with dexamethasone (31 days *vs.* 51 days,  $p=0.221$ ). Multivariate analyses using potential prognostic factors PS, prior history of VZV, baseline beta-2 microglobulin, baseline hemoglobin, baseline platelet count, baseline absolute neutrophil count and absolute lymphocyte count, and prior lines of therapy did not show any factors to be associated with a risk of VZV reactivation, except for bortezomib treatment. Furthermore, the incidence of other infections was similar between the bortezomib arm and dexamethasone arm (12). A Korean group also demonstrated that disease duration, previous herpes zoster infection, disease stage, type of myeloma and the type and intensity of prior treatment, the type of bortezomib-containing regimen, and response to bortezomib treatment were not significantly related to herpes zoster development (21). Thalidomide has not been reported to increase the risk of VZV reactivation (11, 22, 23). These findings indicate that bortezomib plays a specific and important role in VZV reactivation, however, its mechanism remains unclear. Nuclear factor-kappaB has an important role in T-cell immunity (24). Bortezomib inhibits nuclear factor-kappaB and T-cell proliferation (25), which may be one of the mechanisms of bortezomib-induced VZV reactivation.

It is necessary to administer prophylactic antiviral agents because VZV reactivation sometimes results in post-herpetic neuralgia, reduction of quality of life, or even discontinuation of chemotherapy. Although NCCN guidelines for prevention and treatment of cancer-related infections recommend prophylaxis for VZV reactivation in patients receiving bortezomib (18), the optimal doses of antiviral agents and prophylaxis duration have not been described. It is necessary to establish a minimal effective prophylactic dose of antiviral agents in order to reduce the adverse events associated with long-term prophylaxis, *e.g.* neurotoxicity, nephrotoxicity and cytopenia. At first, acyclovir 400 mg three times daily was widely used. Recently, prophylactic effects of low-dose acyclovir (400 mg daily) (13-15), and ultra-low-dose acyclovir (200 mg daily) were reported (16). While acyclovir at a dose of 400 mg daily can almost completely prevent VZV reactivation (13-15), the effects of acyclovir at a dose of 200 mg daily are controversial (15, 16). On the other hand, many investigators

consider that prophylaxis should continue until the cessation of bortezomib treatment (13-17).

Valacyclovir is an oral pro-drug of acyclovir and its bioavailability is three times higher than that of oral acyclovir (26). We use valacyclovir at a dose of 500 mg daily, which has been widely used and well-tolerated by patients with genital herpes simplex viral infection (27). VZV reactivation developed in only one patient during prophylaxis. Although the duration of prophylaxis was long (median=301 days), adverse events over grade 3, associated with valacyclovir, were not observed.

In conclusion, valacyclovir at a dose of 500 mg daily appears to be effective at preventing VZV reactivation and was well-tolerated by patients with MM who received bortezomib. To our knowledge, there are no reports indicating the optimal valacyclovir dose for prophylaxis for VZV reactivation. Large-scale prospective trials should be conducted to confirm whether the valacyclovir dose can be reduced.

## Conflicts of Interest

The Authors declare they have no conflicts of interest.

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